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     FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL' ENTERED AT 15:21:38
ON
     01 SEP 2000
L1          2616 S (T()TYPE) AND CALCIUM AND CHANNEL?
L2           378 S L1 AND MIBEFRADIL
L3            10 S L2 AND INSULIN
L4             6 DUP REM L3 (4 DUPLICATES REMOVED)

=> s amiloride

L5         27053 AMILORIDE

=> s l5 and l1

L6           207 L5 AND L1

=> dup rem l6

PROCESSING COMPLETED FOR L6
L7            86 DUP REM L6 (121 DUPLICATES REMOVED)

=> s l7 and insulin

L8             3 L7 AND INSULIN

=> d l8 ibib abs tot
```

L8 ANSWER 1 OF 3 USPATFULL
ACCESSION NUMBER: 1999:155724 USPATFULL
TITLE: Anti-angiogenic Compositions and Methods for the treatment of arthritis
INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S): Angiogenesis Technologies, Inc., Vancouver, Canada (non-U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5994341	19991130
APPLICATION INFO.:	US 1995-478914	19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Kumar, Shailendra
LEGAL REPRESENTATIVE: Seed & Berry LLP
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 129 Drawing Figure(s); 75 Drawing Page(s)
LINE COUNT: 5044
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions comprising an anti-angiogenic factor, and a polymeric carrier. Representative examples of anti-angiogenic factors include Anti-Invasive Factor, Retinoic acids and derivatives thereof, and paclitaxel. Also provided are methods for embolizing blood vessels, and eliminating biliary, urethral, esophageal, and tracheal/bronchial obstructions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 2 OF 3 USPATFULL
ACCESSION NUMBER: 1999:37140 USPATFULL
TITLE: Anti-angiogenic compositions and methods of use
INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S): Angiotech Pharmaceuticals Inc., Vancouver, Canada (non-U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5886026	19990323
APPLICATION INFO.:	US 1995-472413	19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Kumar, Shailendra
LEGAL REPRESENTATIVE: Seed and Berry LLP
NUMBER OF CLAIMS: 6

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 130 Drawing Figure(s); 75 Drawing Page(s)
LINE COUNT: 997
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions comprising an anti-angiogenic factor, and a polymeric carrier. Representative examples of anti-angiogenic factors include Anti-Invasive Factor, Retinoic acids and derivatives thereof, and paclitaxel. Also provided are methods for embolizing blood vessels, and eliminating biliary, urethral, esophageal, and tracheal/bronchial obstructions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 3 OF 3 USPATFULL
ACCESSION NUMBER: 1998:14828 USPATFULL
TITLE: Anti-angiogenic compositions and methods of use
INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S): Angiogenesis Technologies, Inc., Vancouver, Canada (non-U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5716981	19980210
APPLICATION INFO.:	US 1995-478203	19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Kumar, Shailendra
LEGAL REPRESENTATIVE: Seed and Berry LLP
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 130 Drawing Figure(s); 75 Drawing Page(s)
LINE COUNT: 5084
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides compositions comprising an anti-angiogenic factor, and a polymeric carrier. Representative examples of anti-angiogenic factors include Anti-Invasive Factor, Retinoic acids and derivatives thereof, and paclitaxel. Also provided are methods for embolizing blood vessels, and eliminating biliary, urethral, esophageal, and tracheal/bronchial obstructions.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l8 ibib kwic tot

L8 ANSWER 1 OF 3 USPATFULL
ACCESSION NUMBER: 1999:155724 USPATFULL
TITLE: Anti-angiogenic Compositions and methods for the treatment of arthritis
INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada

PATENT ASSIGNEE(S): Angiogenesis Technologies, Inc., Vancouver, Canada (non-U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5994341	19991130
APPLICATION INFO.:	US 1995-478914	19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Kumar, Shailendra
LEGAL REPRESENTATIVE: Seed & Berry LLP
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 129 Drawing Figure(s); 75 Drawing Page(s)
LINE COUNT: 5044
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . binding of various growth factors such as platelet derived growth factor ("PDGF"), epidermal growth factor ("EGF"), transforming growth factor ("TGF-.beta."), **insulin**-like growth factor ("IGF-1"), and fibroblast growth factor (".beta.FGF"). Suramin may be prepared in accordance with known techniques, or readily obtained. .

.

DETD . . . oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate (i.e., WO.sub.4.sup.2-) complexes include ammonium tungstate (i.e., (NH.sub.4).sub.2 WO.sub.4), **calcium** tungstate (i.e., CaWO.sub.4), sodium tungstate dihydrate (i.e., Na.sub.2
WO.sub.4 .multidot.2H.sub.2 O), and tungstic acid (i.e., H.sub.2 WO.sub.4). Suitable tungsten oxides. . .

DETD . . . one or more hormones such as thyroid hormone, estrogen, progesterone, cortisone and/or growth hormone, other biologically active
molecules such as **insulin**, as well as T.sub.H 1 (e.g., Interleukins-2, -12, and -15, gamma interferon) or T.sub.H 2 (e.g., Interleukins -4 and -10). . .

DETD . . . .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen antiporter (e.g., **amiloride** and its derivatives); agents that modulate intracellular Ca.sup.2+ transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or **T-type** Ca.sup.2+ **channel** blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/**calcium** antiporter (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+ /calmodulin kinase II, casein kinease II); anti-depressants. . .

L8 ANSWER 2 OF 3 USPATFULL
ACCESSION NUMBER: 1999:37140 USPATFULL
TITLE: Anti-angiogenic compositions and methods of use
INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S): Angiotech Pharmaceuticals Inc., Vancouver, Canada (non-U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5886026	19990323

APPLICATION INFO.: US 1995-472413 19950607 (8)
RELATED APPLN. INFO.: Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Kumar, Shailendra
LEGAL REPRESENTATIVE: Seed and Berry LLP
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 130 Drawing Figure(s); 75 Drawing Page(s)
LINE COUNT: 4997
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . binding of various growth factors such as platelet derived growth factor ("PDGF"), epidermal growth factor ("EGF"), transforming growth factor ("TGF-.beta."), **insulin**-like growth factor ("IGF-1"), and fibroblast growth factor (".beta.FGF"). Suramin may be prepared in accordance with known techniques, or readily obtained. .

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DETD . . . one or more hormones such as thyroid hormone, estrogen, progesterone, cortisone and/or growth hormone, other biologically active molecules such as **insulin**, as well as T.sub.H 1 (e.g., Interleukins -2, -12, and -15, gamma interferon) or T.sub.H 2 (e.g., Interleukins -4 and. . .

DETD . . . .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen antiporter (e.g., **amiloride** and its derivatives); agents that modulate intracellular Ca.sup.2+ transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or **T-type** Ca.sup.2+ **channel** blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/**calcium** antiporter (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+ /calmodulin kinase II, casein kinase II); anti-depressants. . .

L8 ANSWER 3 OF 3 USPATFULL
ACCESSION NUMBER: 1998:14828 USPATFULL
TITLE: Anti-angiogenic compositions and methods of use
INVENTOR(S): Hunter, William L., Vancouver, Canada
Machan, Lindsay S., Vancouver, Canada
Arsenault, A. Larry, Paris, Canada
PATENT ASSIGNEE(S): Angiogenesis Technologies, Inc., Vancouver, Canada (non-U.S. corporation)

	NUMBER	DATE
PATENT INFORMATION:	US 5716981	19980210
APPLICATION INFO.:	US 1995-478203	19950607 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1995-417160, filed on 3 Apr 1995, now abandoned which is a continuation-in-part of Ser. No. US 1993-94536, filed on 19 Jul 1993, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1994-CA373	19940719

DOCUMENT TYPE: Utility
PRIMARY EXAMINER: Kumar, Shailendra
LEGAL REPRESENTATIVE: Seed and Berry LLP
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 130 Drawing Figure(s); 75 Drawing Page(s)
LINE COUNT: 5084
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . binding of various growth factors such as platelet derived growth factor ("PDGF"), epidermal growth factor ("EGF"), transforming growth factor ("TGF-.beta."), **insulin**-like growth factor ("IGF-I"), and fibroblast growth factor (".beta.FGF"). Suramin may be prepared in accordance with known techniques, or readily obtained. .
.
DETD . . . oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate (i.e., WO.sub.4.sup.2-) complexes include ammonium tungstate (i.e., (NH.sub.4).sub.2 WO.sub.4), **calcium** tungstate (i.e., CaWO.sub.4), sodium tungstate dihydrate (i.e., Na.sub.2
WO.sub.4.2H.sub.2 O), and tungstic acid (i.e., H.sub.2 WO.sub.4). Suitable tungsten oxides include. . .
DETD . . . one or more hormones such as thyroid hormone, estrogen, progesterone, cortisone and/or growth hormone, other biologically active
molecules such as **insulin**, as well as T.sub.H 1 (e.g., Interleukins-2, -12, and -15, gamma interferon) or T.sub.H 2 (e.g., Interleukins-4 and -10) cytokines.
DETD . . . .alpha.-adrenergic blocking agents, angiotensin II receptor antagonists and receptor antagonists for histamine, serotonin, endothelin; inhibitors of the sodium/hydrogen antiporter (e.g., **amiloride** and its derivatives); agents that modulate intracellular Ca.sup.2+ transport such as L-type (e.g., diltiazem, nifedipine, verapamil) or **T-type** Ca.sup.2+ **channel** blockers (e.g., **amiloride**), calmodulin antagonists (e.g., H.sub.7) and inhibitors of the sodium/**calcium** antiporter (e.g., **amiloride**); ap-1 inhibitors (for tyrosine kinases, protein kinase C, myosin light chain kinase, Ca.sup.2+ /calmodulin kinase II, casein kinase II); anti-depressants. . .

=> d history

(FILE 'HOME' ENTERED AT 15:21:15 ON 01 SEP 2000)

FILE 'MEDLINE, CAPLUS, LIFESCI, EMBASE, USPATFULL' ENTERED AT 15:21:38 ON
01 SEP 2000
L1 2616 S (T()TYPE) AND CALCIUM AND CHANNEL?
L2 378 S L1 AND MIBEFRADIL
L3 10 S L2 AND INSULIN
L4 6 DUP REM L3 (4 DUPLICATES REMOVED)
L5 27053 S AMILORIDE
L6 207 S L5 AND L1
L7 86 DUP REM L6 (121 DUPLICATES REMOVED)
L8 3 S L7 AND INSULIN

=> s l7 and pancrea?

L9 4 L7 AND PANCREA?

=> dup rem l9

PROCESSING COMPLETED FOR L9
L10 4 DUP REM L9 (0 DUPLICATES REMOVED)

=> s l10 not l8

L11 1 L10 NOT L8

=> d l11 ibib abs

L11 ANSWER 1 OF 1 MEDLINE
ACCESSION NUMBER: 97081069 MEDLINE
DOCUMENT NUMBER: 97081069
TITLE: Abnormally expressed low-voltage-activated **calcium channels** in beta-cells from NOD mice and a related clonal cell line.
AUTHOR: Wang L; Bhattacharjee A; Fu J; Li M
CORPORATE SOURCE: Department of Pharmacology, University of South Alabama, College of Medicine, Mobile 36688, USA.
SOURCE: DIABETES, (1996 Dec) 45 (12) 1678-83.
Journal code: E8X. ISSN: 0012-1797.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199703

AB A macroscopic low-voltage-activated (LVA) inward current was found in **pancreatic** beta-cells isolated from NOD mice. However, this current was not present in nondiabetic prone mouse (e.g., Swiss-Webster) **pancreatic** beta-cells. We performed pharmacological analyses on this current in NOD insulinoma tumor cells (NIT-1). This cell line was developed from **pancreatic** beta-cells of a transgenic NOD mouse. The sodium-**channel** blocker, tetrodotoxin (TTX; 2 micromol/l) had no effect on this LVA current. The amplitudes of currents elicited by a -20 mV test pulse retained similarity when the extracellular sodium concentration was increased from 0 to 115 mmol/l; when the extracellular **calcium** concentration was decreased from 10 to 2 mmol/l, there was an approximate 50% reduction of this current elicited by a -30 mV test pulse. Neither the L-type **calcium-channel** blocker, nifedipine (3 micromol/l), nor the N-type **calcium-channel** blocker, omega-CgTx-GVIA (1 micromol/l), at -30 mV produced an appreciable effect. The **T-type calcium-channel** blockers, nickel (3 micromol/l) and **amiloride** (250 micromol/l), effectively reduced the peak of this current. In 2 mmol/l **calcium** external solution, the threshold of voltage-dependent activation of this **calcium** current was approximately -65 mV, and the peak current occurred at -20 mV. Half-maximum steady-state inactivation was around -43 mV. The mean time constant of slow deactivating tail currents generated by a preceding 20 mV pulse was 2.53 ms. The intracellular free **calcium** concentration was two- to threefold higher in NOD mouse **pancreatic** beta-cells compared with Swiss-Webster **pancreatic** beta-cells. We concluded that there are LVA **calcium channels** abnormally expressed in NOD mouse beta-cells. This LVA **calcium channel** may be factorial to the high cytosolic free **calcium** concentration observed in these cells, and thereby may contribute to the pathogenesis of NOD mouse beta-cells.

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NEWS	2	Jun 2	KOREAN PATENTS NOW IN CAS DATABASES
NEWS	3	Jun 20	WIPO/PCT Patents Fulltext Database now on STN
NEWS	4	Jun 28	CAS covers Web-distributed preprints
NEWS	5	Jul 7	Patent Full-text Cluster, PNTTEXT, introduced
NEWS	6	Jul 27	EUROPATFULL - loading of backlog data
NEWS	7	Jul 27	MORE FREQUENT UPDATES FOR DERWENT WORLD PATENTS INDEX IN 2000
NEWS	8	Jul 27	Derwent Journal Of Synthetic Methods Reloaded with New Data
NEWS	9	Jul 27	DERWENT WORLD PATENTS INDEX: FAST TRACK RELEASE OF EQUIVALENT PATENTS
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NEWS	12	Aug 24	TABULATE Now Available in More STN Databases
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FILE 'HOME' ENTERED AT 15:21:15 ON 01 SEP 2000

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FILE 'USPATFULL' ENTERED AT 15:21:38 ON 01 SEP 2000
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=> s (t()type) and calcium and Channel?

L1 2616 (T(W) TYPE) AND CALCIUM AND CHANNEL?

=> s l1 and mibefradil

L2 378 L1 AND MIBEFRADIL

=> s l2 and insulin

L3 10 L2 AND INSULIN

=> dup rem l3

PROCESSING COMPLETED FOR L3
L4 6 DUP REM L3 (4 DUPLICATES REMOVED)

=> d l4 ibib abs

L4 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:191261 CAPLUS
DOCUMENT NUMBER: 132:232751
TITLE: sequence and therapeutic applications for rat pancreatic **T-type calcium channel** as it relates to diabetes
INVENTOR(S): Li, Ming
PATENT ASSIGNEE(S): South Alabama Medical Science Foundation, USA
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000015845	A1	20000323	WO 1999-US19675	19990826

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-98004 19980826
US 1999-117399 19990127

AB The present invention is directed to isolated nucleic acid mols. encoding pancreatic **T-type calcium channels** and vectors and host cells comprising such. The invention is further directed to methods and compns. which modulate the expression of pancreatic **T-type calcium channels**, including antisense. An isolated pancreatic **T-type calcium channel** protein is provided, as well as antibodies directed to such protein. Pharmaceutical compns. and methods of treatment involving pancreatic **T-type calcium channels** are also provided. The pharmacol. of **Mibefradil** action is also discussed and shows that **T-type** Ca2+ current is more sensitive to **mibefradil** than the L-type Ca2+ current in pancreatic .beta.-cells. The results also shows that the inhibitory effect of **mibefradil** on **T-type** Ca2+ current in pancreatic .beta.-cells results from reversible interaction between the drug and the **channel** protein. Inhibition of **T-type Calcium channels** was also shown with a **Mibefradil** metabolite. Further, it was shown that Streptozotocin induced high basal [Ca2+] inhibits KCL stimulated Ca2+ influx. In addn., it was shown that low voltage-activated Ca2+ current mediates cytokine-induced mouse pancreatic .beta.-cell death. The relationship of this gene to NIDDM (non-**insulin**-dependent diabetes mellitus) is described. The data suggest that **T-type calcium channels** are a primary regulator of resting basal [Ca2+] in .beta.-cells. Applications of antisense DNA are revealed which modulate this gene's expression by blocking translation. Expression of a ribozyme is described which results in decreased expression of this rat pancreatic **T-type calcium channel**. Oligonucleotide probes for genomic or cDNA library screening are also described along with monoclonal and polyclonal antibodies. Methods for modulation of L-type **calcium channels** by modifying levels of functional **T-type calcium channels** is also discussed. Lastly, DNA primers are also mentioned to be used in a PCR reaction for amplification of this gene.

REFERENCE COUNT: 4
REFERENCE(S):
(1) Bhattacharjee; Endocrinology 1997, V138(9), P3735 CAPLUS
(2) Eckstein; US 5672695 A 1997
(3) Milner; Nature Biotechnology 1997, V15, P537 CAPLUS
(4) Peres-Reyes; Nature 1998, V391, P896

=> d l4 ibib abs 2-6

L4 ANSWER 2 OF 6 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2000153648 MEDLINE
DOCUMENT NUMBER: 20153648
TITLE: A **mibefradil** metabolite is a potent intracellular blocker of L-type Ca(2+) currents in pancreatic beta-cells.

AUTHOR: Wu S; Zhang M; Vest P A; Bhattacharjee A; Liu L; Li M
CORPORATE SOURCE: Department of Pharmacology, University of South Alabama, College of Medicine, Mobile, Alabama, USA.

CONTRACT NUMBER: DK50151 (NIDDK)
SOURCE: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (2000 Mar) 292 (3) 939-43.
Journal code: JP3. ISSN: 0022-3565.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY WEEK: 200[redacted]0504
AB It has been shown that **mibefradil** (Ro 40-5967) exerts a selective inhibitory effect on **T-type** Ca(2+) currents, although at higher concentrations it can antagonize high voltage-activated Ca(2+) currents. The action of **mibefradil** on Ca(2+) **channels** is use- and steady-state-dependent and the binding site of **mibefradil** on L-type Ca(2+) **channels** is different from that of dihydropyridines. By using conventional whole-cell and perforated patch-clamp techniques, we showed that **mibefradil** has an inhibitory effect on both T- and L-type Ca(2+) currents in **insulin**-secreting cells. However, the effect on L-type Ca(2+) currents was time-dependent and poorly reversible in perforated patch-clamp experiments. By using mass spectrometry, we demonstrated that **mibefradil** accumulates inside cells, and furthermore, a metabolite of **mibefradil** was detected. Intracellular application of this metabolite selectively blocked the L-type Ca(2+) current, whereas **mibefradil** exerted no effect. This study demonstrates that **mibefradil** permeates into cells and is hydrolyzed to a metabolite that blocks L-type Ca(2+) **channels** specifically by acting at the inner side of the **channel**.

L4 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:629439 CAPLUS
DOCUMENT NUMBER: 129:339754
TITLE: Chronic **T-type** Ca2+ **channel** blockade with **mibefradil** in hyperinsulinemic, **insulin**-resistant and hypertensive rats. [Erratum to document cited in CA127:104190]
AUTHOR(S): Verma, Subodh; Bhanot, Sanjay; Hicke, Alan; McNeill, John H.
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, BC, V6T 1Z3, Can.
SOURCE: Cardiovasc. Res. (1998), 40(1), 230
CODEN: CVREAU; ISSN: 0008-6363
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A cor. version of Table 2 is given.

L4 ANSWER 4 OF 6 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998320062 EMBASE
TITLE: Erratum: Chronic **T-type calcium** **channel** blockade with **mibefradil** in hyperinsulinemic, **insulin**-resistant and hypertensive rats (Cardiovascular Research (1997) 34 (121-128) PII: S0008636397000321).
AUTHOR: Verma S.; Bhanot S.; Hicke A.; McNeill J.H.
SOURCE: Cardiovascular Research, (1998) 40/1 (230).
ISSN: 0008-6363 CODEN: CVREAU
PUBLISHER IDENT.: S 0008-6363(98)00170-9
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Errata
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English

L4 ANSWER 5 OF 6 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998368628 EMBASE
TITLE: Life-threatening interaction of **mibefradil** and .beta.-blockers with dihydropyridine **calcium** **channel** blockers.
AUTHOR: Mullins M.E.; Horowitz B.Z.; Linden D.H.J.; Smith G.W.; Norton R.L.; Stump J.

CORPORATE SOURCE: Dr. M.E. Mullins, Mail Code CB 550, 3181 SW Sam Jackson Pa[redacted] Rd, Portland, OR 97201-3098, United States. mu[redacted]nmi@ohsu.edu
SOURCE: Journal of the American Medical Association, (8 Jul 1998) 280/2 (157-158).
Refs: 14
ISSN: 0098-7484 CODEN: JAMAAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB **Mibefradil** is a **T-type** and L-type **calcium channel** blocker (CCB) released in the United States in 1997 for management of hypertension and chronic stable angina. Postmarketing surveillance revealed a potential serious interaction between **mibefradil** and .beta.-blockers, digoxin, verapamil, and diltiazem, especially in elderly patients. The manufacturer voluntarily withdrew **mibefradil** on June 8, 1998. We describe 4 cases of cardiogenic shock in patients taking **mibefradil** and .beta.-blockers who began taking dihydropyridine CCBs. One case resulted in death; the other 3 survived episodes of cardiogenic shock with intensive support of heart rate and blood pressure. Physicians who are preparing to switch patients' medications from **mibefradil** to other antihypertensive agents should be aware of these potentially life-threatening drug-drug interactions.

L4 ANSWER 6 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 97360918 MEDLINE
DOCUMENT NUMBER: 97360918
TITLE: Chronic **T-type** Ca2+ **channel** blockade with **mibefradil** in hyperinsulinemic, **insulin**-resistant and hypertensive rats [published erratum appears in Cardiovasc Res 1998 Oct;40(1):230].
AUTHOR: Verma S; Bhanot S; Hicke A; McNeill J H
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada.
SOURCE: CARDIOVASCULAR RESEARCH, (1997 Apr) 34 (1) 121-8.
Journal code: COR. ISSN: 0008-6363.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710

AB OBJECTIVES: To determine the effects of **calcium** antagonists on hyperinsulinemia, hypertriglyceridemia and hypertension, we examined the long-term effects of a new **calcium channel** blocker, **mibefradil**, on plasma **insulin** levels, plasma triglyceride levels and systolic blood pressure in **insulin**-resistant and hyperinsulinemic fructose-hypertensive (FH) rats. To this aim, both prevention and reversal protocols were employed. METHODS: Prevention study: Male Sprague-Dawley rats were procured at 6 weeks of age and were divided into: control (C, n = 6), control-treated (CT, n = 5), fructose (F, n = 7) and fructose-treated (FT, n = 6). Baseline measurements of plasma glucose, **insulin** and systolic blood pressure were conducted in all groups. At week 7, chronic **mibefradil** treatment (30 mg/kg/day, orally for 6 weeks) was initiated in the CT and FT groups. At week 8, the rats in the F and FT groups were started on a 66% fructose diet to induce hyperinsulinemia and hypertension. Weekly measurements of plasma **insulin**, plasma triglycerides and systolic blood pressure were conducted for the following

4 weeks. Reversal protocol: In a separate study, 8-week-treated FH rats and their age-matched controls were used to examine the effects of **mibefradil** on reversing fructose-induced hyperinsulinemia and hypertension. RESULTS: The F group exhibited hyperinsulinemia (3.2 +/- 0.1 vs. C 2.3 +/- 0.07 ng/ml, P < 0.05), hypertension (148 +/- 3 vs. C 121 +/- 1 mmHg, P < 0.002) and elevated triglyceride levels (5.4 +/- 0.8 vs. C 1.6 +/- 0.3 mM, P < 0.05). Chronic **mibefradil** treatment prevented the development of hyperinsulinemia (1.6 +/- 0.08 ng/ml, P < 0.004 vs. F) and hypertension (123 +/- 1 mmHg. P < 0.001 vs. F) and attenuated the development of hypertriglyceridemia. In the reversal study, **mibefradil** treatment reversed the development of hyperinsulinemia, hypertriglyceridemia and elevated BP in FH rats. Treatment did not affect the plasma glucose levels in any group (prevention or reversal). CONCLUSIONS: Long-term treatment with the **calcium** antagonist, **mibefradil**, both prevents and reverses the development of hyperinsulinemia, hypertriglyceridemia and hypertension in FH rats. These data indicate beneficial effects of **mibefradil** on carbohydrate and lipid metabolism in hyperinsulinemic and **insulin**-resistant states.

=> d all 4

L4 ANSWER 4 OF 6 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
AN 1998320062 EMBASE
TI Erratum: Chronic **T-type calcium** **channel** blockade with **mibefradil** in hyperinsulinemic, **insulin**-resistant and hypertensive rats (Cardiovascular Research (1997) 34 (121-128) PII: S0008636397000321).
AU Verma S.; Bhanot S.; Hicke A.; McNeill J.H.
SO Cardiovascular Research, (1998) 40/1 (230).
ISSN: 0008-6363 CODEN: CVREAU
PUI S 0008-6363(98)00170-9
CY Netherlands
DT Journal; Errata
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
LA English
CT Medical Descriptors:
*error
erratum
priority journal